Is It Time for a Status Update?
Transitioning Treatment from Status Epilepticus to Super Refractory Status Epilepticus

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Pharmacy Grand Rounds
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Objectives

• Differentiate diagnosis of status epilepticus, refractory status epilepticus, and super refractory status epilepticus

• Describe pathophysiology of pharmacoresistance in status epilepticus

• Discuss different treatment options as status epilepticus becomes more refractory
A Silent Epidemic

- 8-19% of comatose ICU patients diagnosed with status epilepticus (SE) on EEG do not have clinical signs of seizures

- Second most common neurological emergency with a risk of major morbidity and mortality
  - Generalized Convulsive Status Epilepticus (GCSE)
  - Non-convulsive Status Epilepticus (NCSE)
    - Negative symptoms
      - aphasia, catatonia, confusion, lethargy
    - Positive symptoms
      - agitation, aggression, delirium, emesis, psychosis

References:
Incidence & Mortality

Question #1

What is the minimum continual seizure duration required to diagnose GCSE?

A. 2 minutes  
B. 5 minutes  
C. 10 minutes  
D. 15 minutes
Classifications

- Status Epilepticus (SE)
- Refractory Status Epilepticus (RSE)
- Super Refractory Status Epilepticus (SRSE)

≥ 5 min of continual seizures without recovery

“Etat de mal”

…”persists for a sufficient time to produce a fixed condition”

- 30 min
- 20 min
- 10 min
- 5 min

Pathophysiology of SE

- Disruption in balance of excitatory and inhibitory neurotransmitters
  - Excitatory: glutamate
  - Inhibitory: GABA
**Stage 1**

**ABC’s**

**LZP**
- 0.1 mg/kg IV
- Max 4 mg/dose
- or

**MDL**
- 0.2 mg/kg IM
- Max 10 mg/dose
- or

**DZP**
- 0.15 mg/kg IV
- Max 10 mg/dose

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Treiman DM, et al. – VA Coop Trial

Successful Treatment (%)

- LZP: 64.9%
- PHB: 58.2%
- DZP+PHT: 55.8%
- PHT: 43.6%

Overt GCSE
Subtle GCSE

p = 0.002

LZP: lorazepam
PHB: phenobarbital
DZP: diazepam
PHT: phenytoin
Out-of-Hospital SE Control

IV LZP: 59.1%  OR: 5.4 (2.3-13.2)
IV DZP: 42.6%
Placebo: 21.1%

IM MDL: 73.4%
IV LZP: 63.4%

LZP: lorazepam
DZP: diazepam
MDL: midazolam

Alternative Routes of Administration

• Intranasal MDL
  • Equally effective as IV DZP in terminating seizures in children

• Buccal MDL
  • More effective than rectal DZP in children with convulsive febrile seizures

• Rectal DZP
  • FDA-approved as Diastat® - 0.2-0.5 mg/kg

Chamberlain JM, et al. JAMA 2014;311(16):1652-60

LZP: lorazepam  DZP: diazepam  MDL: midazolam
Case

• 30 y/o male admitted to the ED for generalized tonic-clonic seizures
  • Continues to seize for over 5 minutes despite two 4mg doses of IV lorazepam
0 min

**Stage 1**

- LZP: lorazepam
  - 0.1 mg/kg IV
  - Max 4 mg/dose
- MDL: midazolam
  - 0.2 mg/kg IM
  - Max 10 mg/dose
- DZP: diazepam
  - 0.15 mg/kg IV
  - Max 10 mg/dose

5 min

**Stage 2**

- ABC’s
- PHT: phenytoin
  - 20 mg/kg IV
- or
  - fPHT: fosphenytoin
    - 20 mg/kg IV PE
- or
  - VPA: valproic acid
    - 20-30 mg/kg IV
- or
  - LEV: levetiracetam
    - 20-60 mg/kg IV

30 min

**Established SE**

>24 hr

**Super Refractory SE**

**Impending SE**
PHT, VPA or LEV?

- Retrospective analysis (n=187)
  - LEV higher risk of failure than VPA
    - OR 2.7, 95% CI 1.2-6.1
  - No difference in PHT
- Largest prospective RCT, single-center comparison

<table>
<thead>
<tr>
<th>AED</th>
<th># controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHT</td>
<td>34/50 (68%)</td>
</tr>
<tr>
<td>VPA</td>
<td>34/50 (68%)</td>
</tr>
<tr>
<td>LEV</td>
<td>39/50 (78%)</td>
</tr>
</tbody>
</table>

No Clear Favorite

- Phenytoin/Fosphenytoin
  - Liver disease, hypotension, QT prolongation, purple glove syndrome, drug interactions

- Valproic Acid
  - Liver disease, pregnancy, hyperammonemia, pancreatitis, somnolence, drug interactions

- Levetiracetam
  - Psychiatric history, agitation, osteoporosis, kidney disease, headache
Case

• 30 y/o male admitted to the ED for generalized tonic-clonic seizures
  • Continues to seize for over 5 minutes despite two 4mg doses of IV lorazepam
  • Continues to seize despite adequate load with fosphenytoin
Can I give another AED?
Definitions

Status Epilepticus (SE)
≥ 5 min of continual seizures without recovery

Refractory Status Epilepticus (RSE)
Seizure activity despite BZD and one AED

Super Refractory Status Epilepticus (SRSE)
Stage 1

- **LZP**: 0.1 mg/kg IV, Max 4 mg/dose
- **MDL**: 0.2 mg/kg IM, Max 10 mg
- **DZP**: 0.15 mg/kg IV, Max 10 mg/dose

Stage 2

- **PHT**: 20 mg/kg IV
- **fPHT**: 20 mg/kg IV PE
- **VPA**: 20-30 mg/kg IV
- **LEV**: 20-60 mg/kg IV

Stage 3

- **MDL**: 0.2 mg/kg load, 0.1-2 mg/kg/hr
- **PRO**: 1-2 mg/kg load, 2-12 mg/kg/hr
- **PBT**: 5-15 mg/kg load, 0.5-5 mg/kg/hr

Additional Information:

- **Brophy GM, et al. Neurocrit Care. 2012;17:3-23**

Legends:

- LZP: lorazepam
- MDL: midazolam
- DZP: diazepam
- PHT: phenytoin
- fPHT: fosphenytoin
- PRO: propofol
- PBT: pentobarbital
- VPA: valproic acid
- LEV: levetiracetam
Midazolam or Propofol for RSE?

• Retrospective chart review (n=20)
  • No difference in seizure control
  • Propofol with APACHE II ≥ 20 had higher mortality

<table>
<thead>
<tr>
<th></th>
<th>Clinical Seizure Suppression (%)</th>
<th>Overall Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDL (n=6)</td>
<td>4/6 (67%)</td>
<td>1/6 (17%)</td>
</tr>
<tr>
<td>PRO (n=14)</td>
<td>9/14 (64%)</td>
<td>8/14 (57%)</td>
</tr>
</tbody>
</table>

p=0.16

Pentobarbital

- Prospective RCT (terminated)
  - Longer ventilation days
  - No difference in seizure activity compared to PRO

- Systematic Review of MDL vs. PRO vs. PBT
  - Less treatment failure (8 vs. 23%, p<0.01)
  - Less breakthrough seizures (12 vs. 42%, p<0.001)
  - More hypotension (77% vs. 34%, p<0.001)

Rossetti AO, et al. Neurocrit Care 2011. 14:4-10
Trinka E, et al. Drugs 2015. 75:1499-1521

PBT: pentobarbital
MDL: midazolam
PRO: propofol
Which anesthetic?

- Insufficient data to support one agent over another

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Metabolism</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>GABA potentiator</td>
<td>Hepatic; active metabolites excreted renally</td>
<td>Short half-life</td>
<td>Hypotension, tachyphylaxis, prolonged elimination half-life in obesity</td>
</tr>
<tr>
<td>Propofol</td>
<td>GABA agonist, Na channel antagonist, NMDA inhibition, Ca channel modulator</td>
<td>Hepatic</td>
<td>Short half-life</td>
<td>Hypotension, PRIS*, hypertriglyceridemia, pancreatitis</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>GABA potentiator</td>
<td>Hepatic</td>
<td>Can be used for prolonged periods</td>
<td>Hypotension, ileus, immunosuppression, hepatotoxicity, metabolic acidosis (propylene glycol toxicity), long half-life</td>
</tr>
</tbody>
</table>

Hocker, SE. Continuum 2015. 21(5):1362-83

*Propofol-related Infusion Syndrome
Case

- 30 y/o male admitted to the ED for generalized tonic-clonic seizures
  - Continues to seize for over 5 minutes despite two 4mg doses of IV lorazepam
  - Continues to seize despite adequate load with fosphenytoin/levetiracetam
  - Continues to seize despite 2mg/kg/hr IV midazolam infusion
Definitions

- **Status Epilepticus (SE)**
  - ≥ 5 min of continual seizures without recovery

- **Refractory Status Epilepticus (RSE)**
  - Seizure activity despite BZD and one AED

- **Super Refractory Status Epilepticus (SRSE)**
  - Breakthrough seizures while on CI anesthetics for 24 hours
**Phase 1: Impending SE**

- **LZP**: 0.1 mg/kg IV Max 4 mg/dose
- **MDL**: 0.2 mg/kg IM Max 10 mg
- **DZP**: 0.15 mg/kg IV Max 10 mg/dose

**Stage 2: Established SE**

- **PHT**: 20 mg/kg IV
- **fPHT**: 20 mg/kg IV PE
- **VPA**: 20-30 mg/kg IV
- **LEV**: 20-60 mg/kg IV

**Stage 3: Refractory SE**

- **MDL**: 0.2 mg/kg load 0.1-2 mg/kg/hr
- **PRO**: 1-2 mg/kg load 2-12 mg/kg/hr
- **PBT**: 5-15 mg/kg load 0.5-5 mg/kg/hr

**Stage 4: Super Refractory SE**

- **Brophy GM, et al. Neurocrit Care. 2012;17:3-23**
Pharmacoresistance of SE

- Increased NMDA receptors
- Decreased GABA receptors
  - 50% decrease in GABA receptors after 1 hour of SE
  - 20-fold decrease in BZD potency within 30 minutes of SE

Ketamine

- NMDA-receptor antagonist
- Animal data endorses efficacy
- Human data suggests safety and efficacy
  - 32% RSE controlled after ketamine
- 1.5-4.5 mg/kg load then 2-7.5 mg/kg/hr
  - Minimum dose response: 0.9 mg/kg/hr
- Earlier it was added, higher chance of control
  - No increase in morbidity or mortality

Lacosamide

- Enhances slow inactivation of sodium channels
- 9 case-series, 10 case-reports
  - No data for RSE
  - 136 patients; 56% success rate
- TRENdS 2013
  - LCM 400 mg vs. fPHT 20 mg/kg for NCSE
  - Terminated in 2014 due to low enrollment

Hofler J, et al. Epilepsia 2013. 54 (3):393-404
Super Refractory Status Epilepticus

• Isoflurane
  • Enhances GABA
  • Case reports show possibly effective when combined with hypothermia
  • Possibly neurotoxic

• Perampanel
  • AMPA-receptor antagonist
  • Case reports suggest variable efficacy
  • Unknown long-term safety profile

Fugate, JE et al. *Anesth Analg* 2010; 111:1520-4
Immunotherapy for SRSE

• SRSE may be caused by antibodies against neural cell receptors
  • IV immunoglobulins (IVIG)
    • 0.4 gm/kg/day x 5 days
  • Methylprednisolone
    • 1 gm/day x 5 days
  • Plasma exchange

Zeiler FA. Seizure 2015. 32:100-108
Super Refractory Status Epilepticus

- **Pyridoxine**
  - Cofactor necessary for GABA production
  - 100-300 mg IV

- **Magnesium**
  - NMDA-receptor antagonist
  - 2-6 gm/hr until level of 3.5 mmol/L
  - 50% controlled in non-eclamptic SE in recent systemic review

- **Neurosurgery if lesion identified**

Glutamate

\[
\text{HO-}\text{C-}\text{NH}_2
\]

GAD, B6

\[
\text{H}_2\text{N-}\text{C-}\text{COOH}
\]

GABA

Zeiler FA. Seizure 2015. 32:100-108
Review

- Benzodiazepines to stop initial seizure
- Load with an AED to prevent future seizure
- Repeat different AED if remain in NCSE with consciousness; transition to anesthetics more quickly if in GCSE
- Choose anesthetics based on comorbidities and drug properties
- Kitchen sink
Question #2

• Which of the following underlying mechanism(s) of SRSE makes ketamine an attractive option?
  A. Increased sensitivity of GABA receptors
  B. Increased number of GABA receptors
  C. Increased number of NMDA receptors
  D. All of the above
Question #3

• When compared to propofol and midazolam, which of the following is a disadvantage of pentobarbital for RSE?
  A. Development of tachyphylaxis
  B. Increased incidence of hypertriglyceridemia
  C. Likelihood of developing rhabdomyolysis
  D. Profound hypotension
Summary

• Seizure duration and failure of treatments differentiate the stages of status epilepticus

• Agents used early may no longer be effective due to development of pharmacoresistance

• Increased morbidity and mortality as status epilepticus becomes more refractory

• Treat quickly; time is brain
Questions & Discussion
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